

Remarks

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendment, claims 41-45 are pending in the application, with 41 being the only independent claim. Claims 22-40 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 41-45 are believed to read on the elected invention, and are sought to be added.

The amendments to the specification are merely formal in nature, and are not believed to introduce any new subject matter.

Support for new claims 41-45 can be found in Applicants' specification. The general principles of the "two-part" method of the new claims are described, for example, on page 9, second paragraph, to page 10, line 20, of the specification. Moreover, a detailed description of the "two-part" method is provided in Example 3 on pages 13-16 of the specification (see particularly page 14, line 19 to page 15, line 4). In this Example, a semi-purified preparation containing both (i) clostridial holotoxin and (ii) toxin fragments, is applied to first affinity column comprising a first ligand (in this case an antibody) that selectively binds to the holotoxin but not to the toxin fragment. The eluate from this first affinity column is then applied to a second affinity column comprising a second ligand (in this case Protein G), wherein the second ligand selectively binds to any ligand-toxin complex that had leached from the first column.

It is clear from the description that the first ligand can alternatively comprise a metal ion (see page 7, line 25 to page 8, line 4 of the specification; see also Example 4 on pages 16-17 of the specification). Similarly, the second ligand can alternatively comprise an antibody (see page 10, line 11 of the specification). Indeed, the first ligand can

comprise any molecule that selectively binds to the clostridial toxin, and the second ligand can comprise any molecule that selectively binds to ligand-toxin complex that has leached from the first column.

Hence, none of the changes or additions are believed to introduce new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Specification

The Examiner has objected to the specification regarding its format or arrangement, and regarding its reference to "Fig. 1." Office Action, pages 3-4. Applicants have adopted the suggestions made by the Examiner and made amendments to the specification. Applicants also note that a preliminary amendment filed on March 12, 2002 provided an Abstract on a separate page. Accordingly, Applicants believe that the objections have been rendered moot, and respectfully request that they be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112

Claim 37 and its dependent claims are rejected under 35 U.S.C. § 112, first paragraph for allegedly constituting new matter. Office Action, page 5. In light of the claim amendments made herein, Applicants believe that the rejection is now rendered moot. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection.

Claims 22-30 and 37-40 are rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Office Action, pages 6-7. In light of the claim amendments
Atty. Dkt. No. 1581.0900000/RWE/ALS

made herein, Applicants believe that the rejection is now rendered moot. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 102

Claims 22-24 and 27-29 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Rossetto *et al.* Office Action, page 8. Applicants respectfully traverse the rejection. However, in order to expedite prosecution (and not in acquiescence to the rejection), Applicants have amended the claims and believe that the rejection is now moot.

Moreover, a *prima facie* case of anticipation is not set forth unless the applied reference teaches all of the claim limitations. *See* M.P.E.P., 8th ed., §2131 (rev. 2, May 2004). Applicants note that Rossetto *et al.* does not teach a method comprising a first affinity column and a second affinity column as recited by the amended claims.

Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 103

Claims 25 and 26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rossetto *et al.* in view of Hallis *et al.* Office Action, pages 8-9. Applicants respectfully traverse the rejection. However, in order to expedite prosecution (and not in acquiescence to the rejection), Applicants have amended the claims and believe that the rejection is now moot.

Moreover, a *prima facie* case of obviousness is not set forth unless the applied references teach or suggest all of the claim limitations. *See* M.P.E.P., 8th ed., §2143.03

(rev. 2, May 2004). Applicants note that Hallis *et al.* does not cure the deficient teaching of Rosetto *et al.*

Applicants also note that there is no recognition in the prior art of any leaching of the bound ligand-toxin complex from an affinity column.

Prior to Applicants' invention, there was a need for highly purified preparations of clostridial toxin fragments for use in, for example, the manufacture of vaccines against clostridial-based diseases. *See* specification, page 3, lines 9-16. Methods for purifying preparations containing clostridial toxin fragments were known prior to Applicants' invention, however there was a significant risk of *residual toxicity* associated with these methods (see page 4, lines 19-23 of the specification).

One such method involved running a preparation of digested clostridial holotoxin through a chromatography column. The column comprised a ligand that bound the clostridial holotoxin (forming a ligand-toxin complex), but that let the clostridial toxin fragments run freely through the column (i.e. elute). For the purposes of the present invention, however, the preparation of clostridial toxin fragments that resulted from this method had an unacceptably high residual toxicity.

The key to solving this problem lay in the realization that the residual toxicity was the result of a small amount of leaching of the above-mentioned ligand-toxin complexes from the chromatography column. These leached or detached complexes were collecting in the column eluate, together with the purified fragments, and were eventually breaking up and releasing toxin into the preparation – hence causing the residual toxicity.

Thus, the prior art did not even appreciate that conventional purification methods were inadequate (in terms of efficient toxin removal) when highly pure preparations were

required (e.g. for vaccine applications). Accordingly, at the time of Applicants' invention, there was no incentive to improve the conventional purification methods, and there was absolutely no teaching or suggestion of a second affinity column (or, a "two-part" system) as recited by the present claims.

Having identified the problem as the leaching of the ligand-toxin complexes from the column, the Inventors devised a "two-part" toxin removal method, wherein the eluate from the first column (essentially as described above) was run through a second column, in which a second ligand was used to selectively bind the leached ligand-toxin complexes, while, again, letting the toxin fragments run freely through the column.

This "two-part" method was found to be extremely effective at removing clostridial toxin from a preparation, as confirmed by the experiments described at page 10, lines 14-20 of the specification.

Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection.

Conclusion

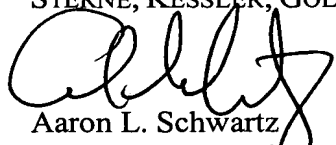
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will

expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read 'A. Schwartz', is written over the printed name.

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